Spinal Cord Lesions

Introduction

You must be able to go from diagnosis to symptoms and from symptoms to diagnosis. This is a game with strict rules and very few players. This is all information you've seen before, discussed briefly and integrated, removing the detail contained in two previous lessons. This is a game of tracts and nuclei. And although the central nervous system in the cranium is fair game, we have simplified this lesson to be strictly about the spinal cord.

The players:

In the **corticospinal tract** (the motor tract), there are the upper and lower motor neurons. The **upper motor neurons** have their cell bodies in the cortex, with their axons running through the posterior limb of the internal capsule. Those **axons decussate** at the medulla and descend the spinal cord to synapse on the lower motor neuron in the **anterior horn** of the spinal cord. The **lower motor neurons** have their cell bodies in the anterior horn of the spinal cord, receive inputs from the upper motor neurons, and project their axons into the peripheral nerve to innervate the muscle. In the spinal cord, there is either a lesion of the tract (upper motor neuron symptoms) or a lesion at the level of the lower motor neuron (lower motor neuron symptoms).

In the **DCMLS**, there are peripheral sensory neurons in the dorsal root ganglia, derived from neural crest cells, which have bifurcated axons—one side projects out into the periphery, and the other synapses onto a sensory neuron in the posterior horn. Those neurons project axons that ascend the spinal cord in the dorsal columns. They carry general touch sensation—vibration, proprioception, pressure. Their axons ascend the **ipsilateral** dorsal columns until the medulla, where they synapse on neurons in their corresponding nuclei (the fasciculus gracilis synapses on the gracilis's nucleus, the cuneate fascicle synapses on the cuneate's nucleus). The neurons of the medullary nuclei have axons that immediately decussate and ascend as the medial lemniscus to the VPL of the thalamus (focus on "thalamus" and not "VPL"). Thalamic nuclei project to the primary somatosensory cortex through the posterior limb of the internal capsule.

In the **STT**, there are peripheral sensory neurons in the dorsal root ganglia, derived from neural crest cells, which have bifurcated axons—one side projects out into the periphery, and the other synapses onto a sensory neuron in the posterior horn. At the same vertebral level, those neurons in the posterior horn **decussate** across the anterior of the spinal canal, find their place in the lateral STT, and ascend on the **contralateral side** to the VPL of the thalamus.

The **spinal cord** is within the **spine**, protected by the bones of the vertebrae it runs through. **Peripheral nerves** are combinations of multiple different tracts' axons running together. **Spinal cord nuclei** of a given tract are distributed throughout the spinal cord, a continuous column of neurons. **Spinal cord tracts** are the axons of the tract, either projecting from cortex down to the spinal cord nuclei or up from the periphery. The spinal cord tracts are contained in fascicles. Fascicles are bundles of axons and the glial cells that care for them. While an action potential may travel within an axon, the axons are always present. They have mass and take up space. The parenchyma of neural tissue is lined with ependymal cells around the CSF-filled spinal canal, and the spinal cord is surrounded by the leptomeninges (pia mater, subarachnoid space, and arachnoid layer), encased in dura mater, and protected by the bone of the vertebrae. The arrangement is the same as in the cranium, except there is a gap at every vertebral level, space to project the fibers of every tract into the peripheral nerve.

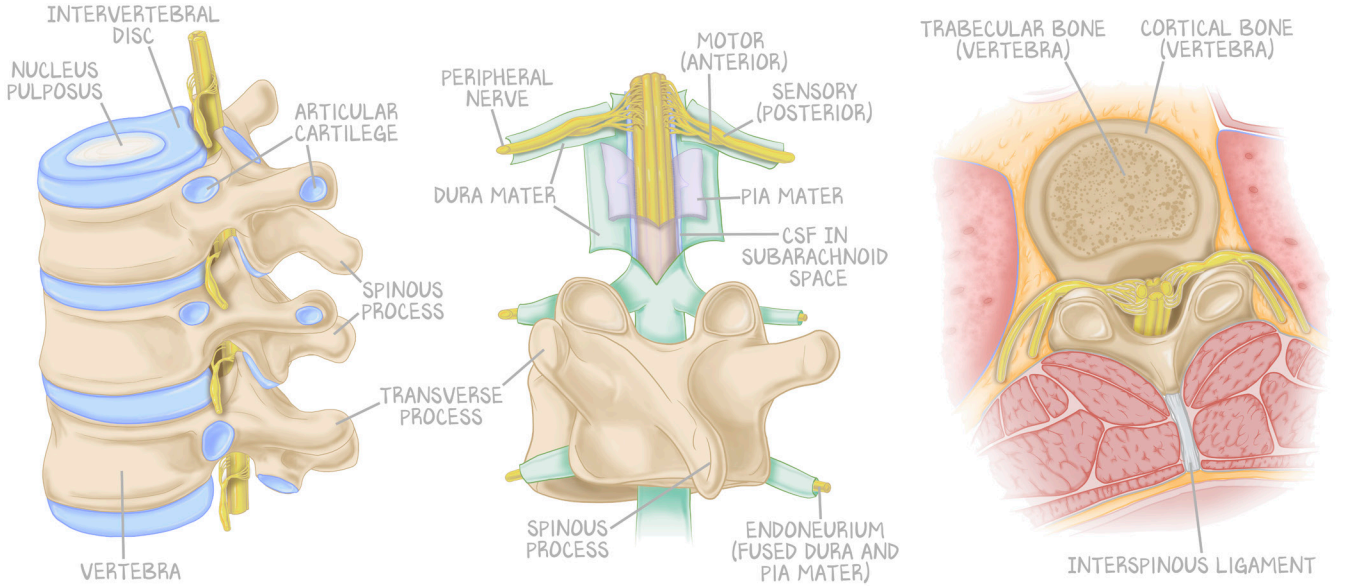

Figure 3.1: Overview of the Anatomy of the Spine and Spinal Cord
In the first image, the emphasis is on the intervertebral discs and the vertebrae. The discs contain the inner nucleus pulposus (the remnant of the notochord) and serve to keep bone from grinding on bone. They also provide space for the fascicles of every tract to exit the spinal cord and meet the dorsal root ganglion axons to form the peripheral nerves. The fascicles need to exit, and the intervertebral discs create gaps between the vertebrae for the nerves to exit. The center image focuses on the dura and leptomeninges. Just as in the skull, dura mater surrounds the arachnoid mater, the arachnoid mater is continuous with the pia mater through trabeculae, and between the trabeculae is the CSF-filled subarachnoid space. The third image provides a cross-section to show the arrangement of cortical and trabecular bone in the vertebrae and how the peripheral nerves exit as discrete fascicles (one for each tract, sensory in back, motor in front) that converge to form the peripheral nerves.

The Rules:

If there is a lesion of the spinal cord that compromises axons, that lesion claims the entire tract below the lesion, and anything above the lesion is retained. If there is a lesion of the spinal cord that compromises nuclei (claims neuron cell bodies), the effect is felt at that vertebral level. But almost always in the spinal cord, a loss of neurons at a given level also means loss of the tract below it. Because exceptions are so rare, we want you to think, "*if axons are lost, then the tract below is lost. If neurons are lost, then that level and the tract below are lost.*"

For lesions of the corticospinal tract (motor), the symptom will be **weakness**, either decreased strength or total paralysis. An **upper motor neuron lesion** will always demonstrate hyperreflexia, increased tone, and upward-flaring toes on a Babinski reflex test. A **lower motor neuron lesion** will always demonstrate hyporeflexia, fasciculations, and atrophy. The Babinski reflex test is unreliable, but because the rules are that the loss of a nucleus means loss of the tract below it, unless there is some lesion of the peripheral nerve itself, there will be upward-flaring toes. Adults' toes normally curl down, but flare upward with upper motor neuron lesions, and show no movement if the peripheral nerve is severed.

For the DCMLS, licensing exams will vary cases by which touch sensation is lost, to keep you on your toes, but there won't be incongruent findings (such as loss of vibration sense but intact proprioception). It's just that some symptoms will be omitted. All symptoms will involve vibration, 2-point discrimination, light touch, pressure, proprioception, or a combination thereof.

For lesions of the STT, there will be a loss of **pain** or **temperature** sensation.

Lesions will either be **above the medulla** (contralateral pain, contralateral touch, and contralateral motor) or be **below the medulla** (contralateral pain, ipsilateral touch, and ipsilateral motor).

Lesions go **down**, never up. Because these tracts run to or from the cortex, damage to one vertebral level compromises the axons of all those below. Those above are left unaffected. At the level of the lesion, neurons die. Justify this by visualizing the tracts as moving from start to finish. At the lesion, things die. As the sensory axons below the lesion rise, they encounter the lesion—a roadblock. They collide with the lesion and disintegrate (not really, but the visualization makes it clear; any signal from below is not going to reach the cortex). Above the lesion, new sensory axons enter the tract, never aware of the lesion below. In reverse, the motor axons descend. Motor axons that terminate proximal to the lesion never encounter the lesion. Those that travel down into the lesion are blocked from going farther; they collide with the lesion and disintegrate (not really, but the visualization makes it clear; any signal from above is not going to reach the lower motor neuron). The visualization of "disintegrating on a roadblock" usually helps learners easily deduce the result of a lesion.

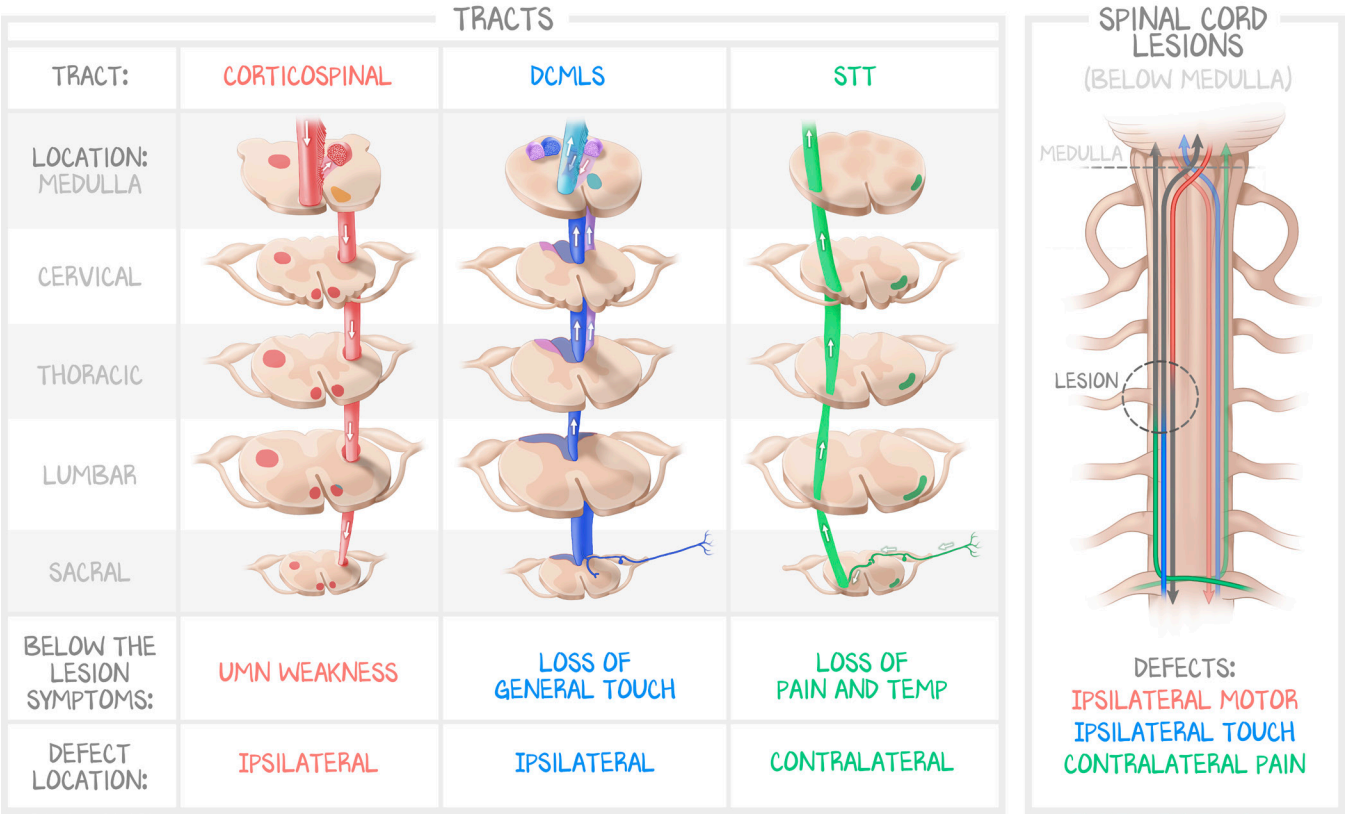

Figure 3.2: Tracts and Lesions, the Rules of This Game
Because we are focused on only the spinal cord, and there are no lesions above the brainstem, the spinothalamic tract will always have crossed below the lesion and, therefore, will always affect the contralateral side. Because no axons of the corticospinal tract or DCMLS will have crossed, the lesion always causes ipsilateral loss of general touch, lower motor neuron symptoms at the level of the lesion, and upper motor neuron symptoms below the lesion.

The Game

Round 1 (Warmup): Brown-Séquard Syndrome

If the spinal cord is perfectly transected, a perfect **hemisection**, there will be a complete loss of one half of the spinal cord. A perfect transection of the spinal cord is truly only seen in experimental models where the incision is made intentionally. But this lesion so clearly assesses a learner's knowledge of nuclei and tracts that it is commonly used on licensure exams, in the context of knife or gunshot wounds. In

this case, an individual is stabbed with a long, immensely sharp knife with incredible precision while fully flexed (to avoid the spine). A complete hemisection occurs at T2. What are the symptoms at T6?

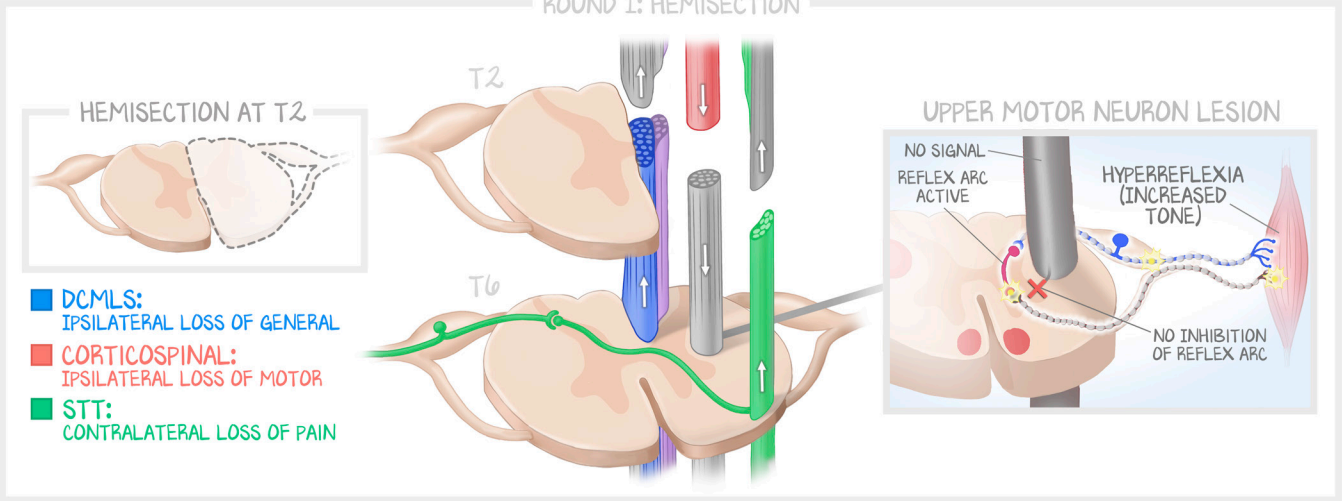

Figure 3.3: Round 1—Hemisection
The question asks about T6, below the lesion. Take your spinal cord. Visualize your tracts. The DCMLS starts ascending from below and crosses in the medulla (so has not yet crossed). The axons below the lesion collide with the lesion and disintegrate. Axons above the lesion are added to the fascicle as normal. Ipsilateral touch sensation is lost below the lesion. The STT starts ascending from below after immediately crossing at the vertebral level it entered. Axons below the lesion collide with the lesion and disintegrate. Axons above the lesion are added to the fascicle as normal. Contralateral pain and temperature sensation are lost below the lesion. The corticospinal tract has already crossed in the medulla. Its axons leave the fascicle to innervate motor neurons above the lesion. What's left hits the lesion and disintegrates. That means that there will be ipsilateral upper motor neuron symptoms below the lesion.

Round 2: Anterior Spinal Artery Syndrome

The **vertebral arteries** originate from the subclavian artery, enter the transverse foramen of the C6 vertebra, then ascend through successive foramina (we want this word to be foramens, but it's not) to the base of the skull. There, they move anterior to the brainstem and ascend into the skull. More details on this come later when we get to the brainstem. Right now, we want you to focus on the spinal arteries. We're also eliminating variations (there are a lot from person to person) to make this manageable.

At the base of the brainstem, at the bottom of the medulla, the vertebral arteries project three smaller arteries back down the spinal cord. Both vertebral arteries contribute to the **one anterior spinal artery**, which will traverse the entire length of the spinal cord. Each vertebral artery produces a posterior spinal artery, meaning that **two bilateral posterior spinal arteries** will traverse the length of the posterior spinal cord. There is an anastomosis between the two posterior spinal arteries, but not one between the posterior arteries and the anterior spinal artery. The one anterior spinal artery is responsible for the perfusion of the **anterior two-thirds of the spinal cord**. The posterior horns and the DCMLS are irrigated by the posterior spinal arteries. Everything else is handled by the anterior spinal artery. The vertebral arteries ascend (and we'll talk about that in the brainstem lessons).

Along the length of the spinal cord, these arteries get "re-upped" (supplied with additional blood) by some vessel. At each level of the spine, a different artery perfuses the nerve roots and re-ups one of the spinal arteries. We're going to use the posterior intercostal artery in the following description, but it is merely a stand-in for any artery that supplies the segmental spinal arteries. In the T-spine, the **posterior intercostal arteries'** first branch is called a **segmental spinal artery**. Each segmental artery, on each side, will *at least* produce **radicular arteries**—arteries that supply the nerve roots (the posterior

radicular artery perfuses the dorsal sensory root; the anterior radicular artery perfuses the anterior motor root)—but do not connect with an anterior or posterior spinal artery. Sometimes the segmental spinal artery has a super-radicular artery, one that anastomoses with either the anterior spinal artery or the posterior spinal artery. When one does, it is named a **segmental medullary artery**. If the radicular artery reaches out and re-ups the anterior spinal artery, it is called an anterior segmental medullary artery. If the radicular artery reaches out and re-ups one of the posterior spinal arteries, it is called a posterior segmental medullar artery. The "medullary" part has nothing to do with the medulla oblongata; it is a modifier that means, *"reaches farther and creates an anastomosis with the spinal arteries."* There are typically 8–10 segmental medullary arteries on either side of the spine.

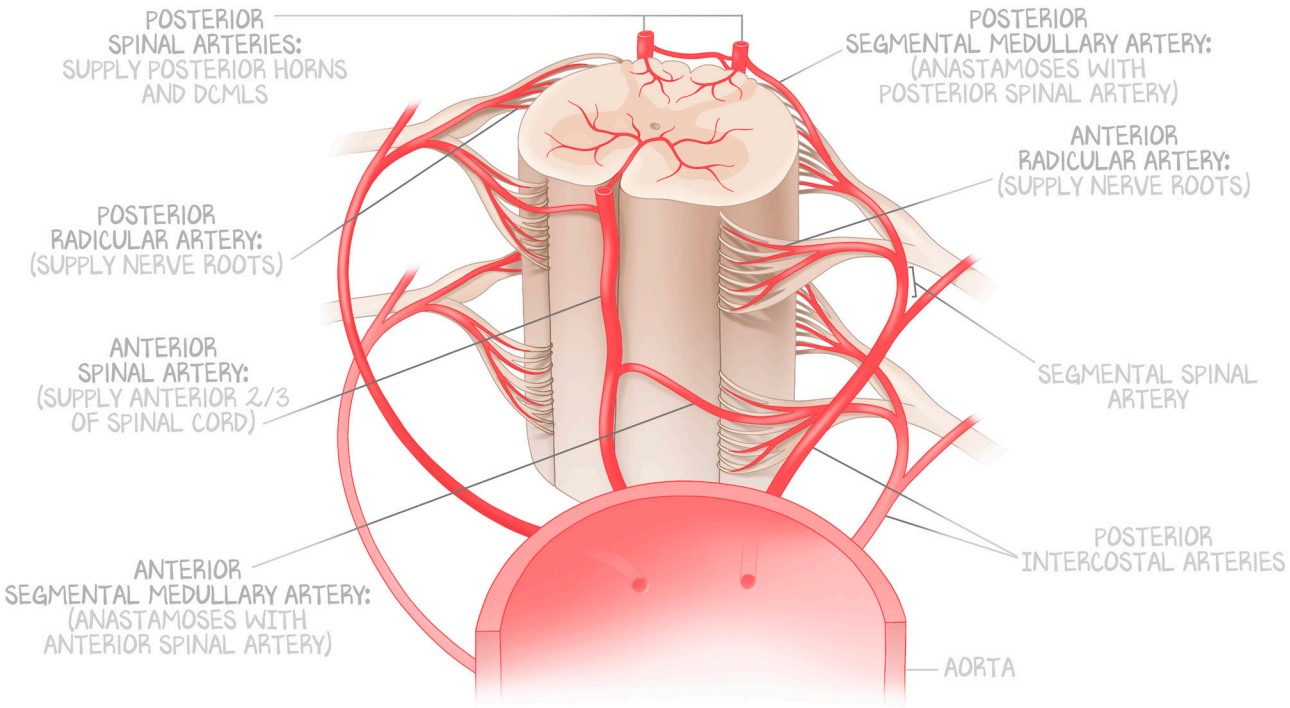

Figure 3.4: Round 2—Spinal Arteries I—Naming the Spinal Arteries
This illustration serves to identify the anterior spinal artery (one) and the two posterior spinal arteries. It also demonstrates how the various branches are named. Some artery (here in the thoracic region, one of the posterior intercostal arteries) produces a segmental spinal artery that quickly divides into anterior and posterior branches. Those branches are at least radicular arteries (supply the nerve roots). Sometimes, those radicular arteries go farther and "re-up" the anterior or one of the posterior spinal arteries. When a radicular artery goes farther, it is called a segmental medullary artery (posterior if re-ups a posterior spinal artery, anterior if it re-ups the anterior spinal artery).

The **midcervical** spinal cord receives segmental spinal arteries from the **vertebral arteries**. Between C7 and T1 (crossing from cervical into thoracic vertebrae), there is a **radiculomedullary** artery from the aorta. There is only one of these arteries for both the anterior and posterior spinal arteries across two vertebral levels. In the **thoracic vertebrae**, segmental arteries are generated from the **posterior intercostal arteries**. Between T8 and L2 (crossing from thoracic into lumbar vertebrae), there is a **radiculomedullary** artery with the eponym, the "*artery of Adamkiewicz*." There is also only one of these arteries for both the anterior and posterior spinal arteries across two vertebral levels—more on this in the next paragraph. The **lumbar** spinal cord is irrigated by segmental arteries that arise from the **lumbar** arteries.

The point of this is that the arterial supply to the spine has amazing redundancy. With so many anastomoses, it is extremely difficult to have a vascular event. Any blockage in one artery can be perfused on either side of the blockage from the anastomosis. But did you notice where the radiculomedullary arteries arise? Where the C-spine turns to T-spine and where the T-spine transitions to L-spine. That isn't a convenient coincidence, but rather it demarcates where the spinal segmental arteries originate—vertebral arteries to posterior intercostal, posterior intercostal to lumbar. The radiculomedullary arteries originate from the aorta, and they aren't "re-ups" at all; they **are the anterior spinal blood supply**. The Adamkiewicz artery (AKA) has the greatest variation in location and anatomy. In patients in whom the AKA has a larger caliber than the anterior spinal artery, there is the greatest risk of neurologic damage if the AKA is lesioned, because it is considered an end artery, making its vascular territory a **watershed area**.

In trauma, iatrogenic injury during repair of the **thoracoabdominal aorta** (dissection, hematoma, aneurysm), or systemic hypotension, the AKA can become compromised. There is generally no communication or anastomosis between the anterior and posterior spinal arteries, thus making the AKA similar to an end artery. This vascular anatomy can often lead to anterior spinal cord syndrome within the region of the lumbar spinal cord. Diagnosis is made by MRI, which can show the classic "owl's eyes" hyperintensity on T2-weighted axial imaging.

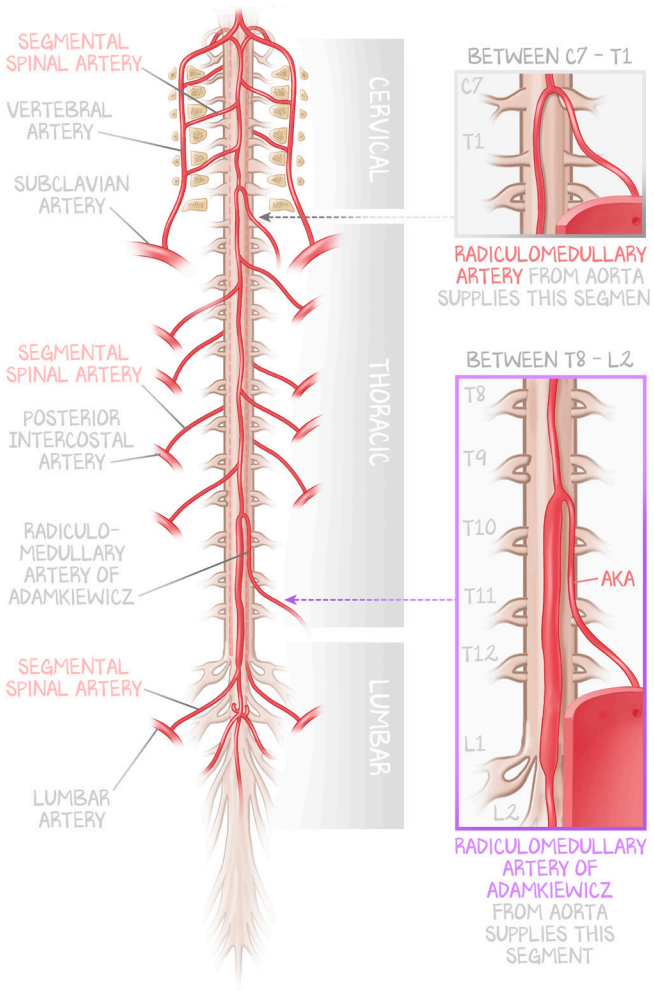

Figure 3.5:

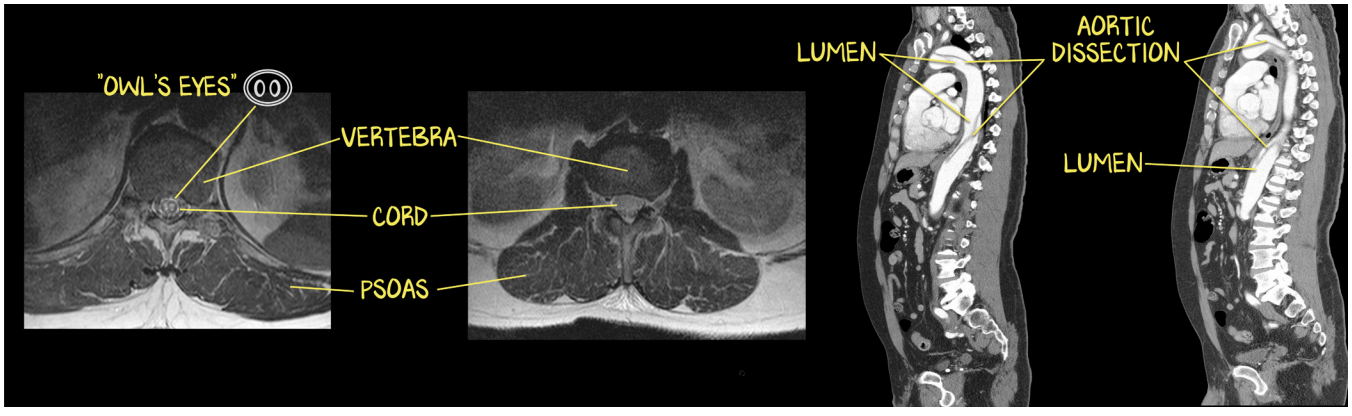

Figure 3.6: A look at Adamkiewicz Artery Syndrome Through Radiographs
The diagnosis is super subtle because the spinal cord is so small. You can see the spine of the vertebral process posterior, the vertebral body (it may also be a disc at this view), and the cord between. The "owl's eyes" are the side-by-side grey ovals within the cord. The ascending and descending aortic dissection that caused it, on the other hand, is quite obvious.

If the AKA were compromised, a spinal infarct could result. If there were a complete spinal cord infarct in the territory of the AKA, what would the symptoms be at the level of the infarct?

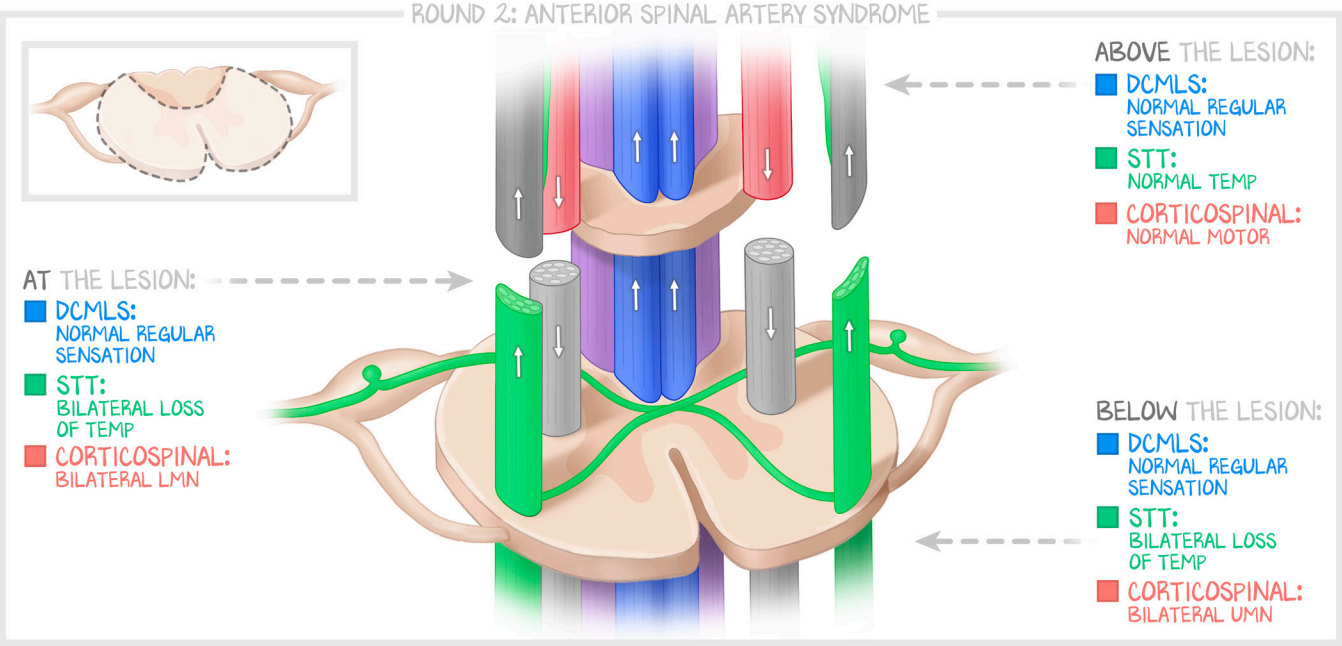

Figure 3.7: Round 2—Anterior Spinal Artery Syndrome
Due to the bilateral loss of the corticospinal tract and nuclei, there will be lower motor neuron symptoms at the level of the infarct and upper motor neuron symptoms below the infarct bilaterally. Due to the bilateral loss of the STT and its nuclei at the level of the infarct, there will be no sensation of pain or temperature from the level of the infarct down. The DCMLS is spared, so touch sensation and proprioception remain intact.

Did you check your interrogatory? Because it specifies, *at the level of the infarct*. This was done intentionally to remind you to watch out for the interrogatories on licensing exams. The predominant syndrome would be that of the upper motor neuron lesions—the infarct compromising all upper motor neuron synapses from the lesion down, while only at a discrete level (at the lesion).

Round 3: Going the Other Way

A 52-year-old male is seen for frequent falls. He feels as though he cannot find himself in space and keeps tripping on the edges of door stops, curbs, and even flat ground. As he walks, you observe a wide-based gait. When you ask him to close his eyes and maintain his balance, he loses balance and starts to fall. He has decreased sensation to vibration and light touch on his legs bilaterally. His strength is normal, as are deep tendon reflexes. He has intact sensation to cold temperatures bilaterally. He fails to coordinate his heel and shin. He has a history of sexually transmitted infections in his early youth.

The diagnosis is tabes dorsalis, caused by tertiary syphilis. The diagnosis doesn't matter. Reverse engineer the lesion—what structures are affected? His strength and reflexes are intact bilaterally, so the corticospinal tracts are intact. He has normal sensation to cool temperatures, indicating the STT is intact. The lack of proprioception (failed heel to shin, loss of balance with eyes closed) and light touch and vibration sensations bilaterally indicates that the lesion is in the spinal cord and involves a loss of the bilateral DCMLS.

Round 4: Vitamin B_{12} Deficiency

Vitamin B_{12} (cobalamin) is necessary for myelin synthesis (as well as a lot more learned in the Heme/Onc module's lesson on anemia). The anemia will present first, but given enough time, subacute combined degeneration of the cord will result. Initially, there will be severe bilateral impairment of proprioception and vibration sensation. If untreated, it will claim more of the spinal cord, leading to ataxia and bilateral

spastic weakness. The symptoms tend to be worse in the more distal segments, affecting the feet. Sensation to temperature and pain remain unaffected. Draw a spinal cord and mark the lesions.

Subacute combined degeneration of the cord affects the dorsal columns (DCMLS) and the corticospinal tract. This was an opportunity for you to get more field time in this game we have been playing, but also an opportunity to expand beyond the rules of the game. If you marked DCMLS and CST, good job. But there is more to it than that, and we want you to take a little something extra from this case. Namely, ataxia may be caused by a lesion to the spinocerebellar tract, which happens as the disease advances. The spinal cord tells the cerebellum where things are. The brain never sees that signal but does hear its outcome (more on this in the lesson on the brainstem). Without the input to the cerebellum, the cerebellum cannot adequately hear the peripheral signal, and so cannot send back appropriate motor instructions, nor can it send good information to the cortex to continue the movement. We'll go into more depth when we get to the cerebellum. Lastly, the dorsal root ganglion is impaired, compromising all sensation.

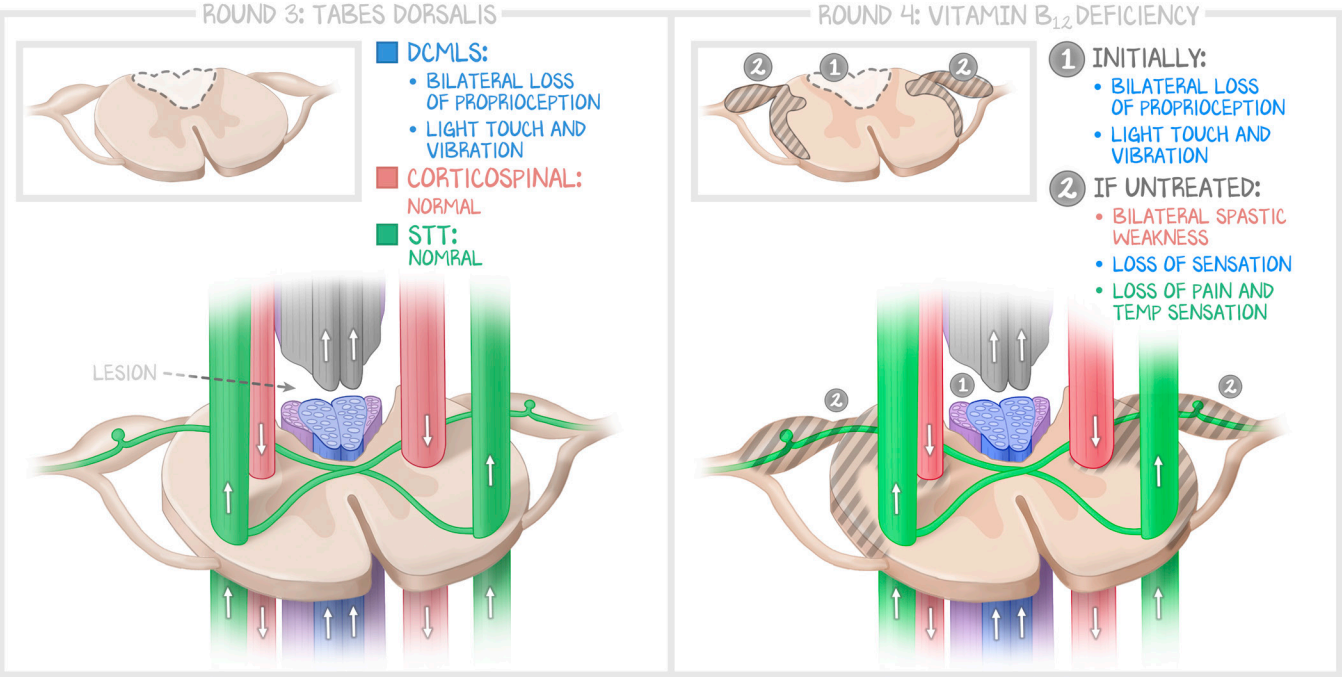

Figure 3.8: Rounds 3 and 4—DCMLS Conditions
Round 3 saw a loss of the DCMLS secondary to tabes dorsalis. It tends to affect the more distal DCMLS first; thus, normal fibers are still entering "above the lesion." In Round 4, subacute combined degeneration of the cord starts with the most distal DCMLS, presenting like tabes dorsalis. If left unattended and uncorrected, the damage will progress to include the STT and its nuclei as well as the corticospinal tract.

Round 5: Syringomyelia

Although it's not a super common diagnosis (8 in 100,000, so it's actually super rare), a syrinx beautifully illustrates the concept of crossing fibers. In syringomyelia (a generic term for "cyst in the spine"), a syrinx (a "cyst" or fluid-filled sac) forms in the spinal canal. This is almost always a childhood disease, occurring in patients who already have malformations of their foramen magnum, such as Dandy-Walker or Chiari malformation type 1. Acquired syringomyelia can occur following spinal surgery or as a product of infection—either meningitis or encephalitis. No matter how it forms, a cyst forms in the spinal canal and erodes into the spinal cord. The glial cells know this cyst is no good, as the cyst is often coated in activated glial cells, a term called **gliosis**. There will be **activated microglia** (which

look like macrophages), oligodendrocytes, and astrocytes. This cyst forms slowly, and usually near the foramen magnum, affecting the spinal canals of C2, C3, and C4. It erodes into the **anterior commissure** of the STT. The STT sensory nuclei are present in the posterior horn, and their axons cross at their level and then ascend to the thalamus. They cross at the anterior commissure. The syrinx does not erode far enough to reach the tracts themselves—they are too lateral. This means that, unlike in some of the other diagnoses we've talked about, the symptoms present only at the level of the lesion. With the CST and DCMLS spared, what do you think the symptoms of this condition are?

Bilateral segmental loss of pain and temperature in a "cape-like" distribution. It is bilateral because both the left and right second-order neurons' axons decussate here. It is segmental because the cyst is larger and more advanced superiorly, so C2 is affected more than C3, which is more affected than C4. The dermatomal distribution of those nerve roots is on the neck and shoulders, so it is "cape-like." Most importantly, only the STT is compromised, so the sensations of pain and temperature are compromised. Those that are acquired can occur anywhere and won't be cape-like. Congenital occurrences affect the area near the defect.

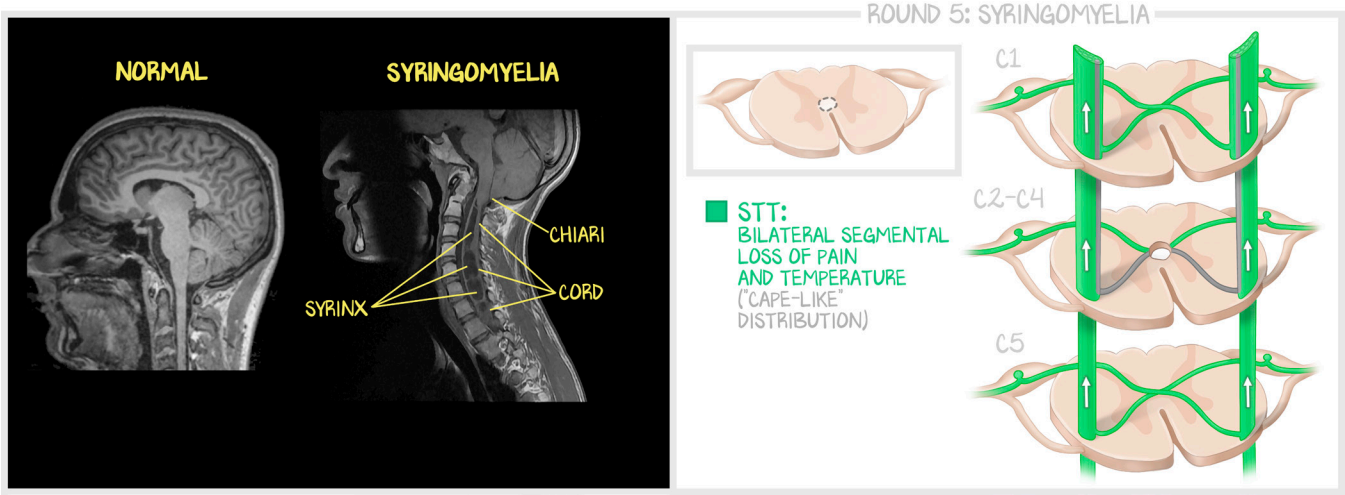

Figure 3.9: Syrinx
The left panel shows a normal MRI as compared to an MRI from a patient with Chiari malformation type I and a holocord presentation of the syrinx. The syrinx has replaced nearly the entire cord. This is an absurdly rare condition, and certainly would have no "cape-like distribution." The illustration (right) demonstrates intact tracts and axons above and below the lesion, but the loss of the axons that cross. Notice C2–C4 is merely representational—below is ok, above is ok, but at the level of the lesion, bilateral pain sensation and temperature are lost.

Round 6: Cauda Equina Syndrome

The spinal cord functions as both a pathway for organized tracts from the cortex and a site where neurons of various tracts can be assembled into terminal nerves. During the fetal period, growth in the length of the spinal cord lags behind that of the vertebral column, thus pulling the nerve roots and leaving the end of the spinal cord as a cauda equina. The **conus medullaris**, the end of the spinal cord, is usually found around L2. The conus represents the end of the distinct spinal cord and the tapering of the spinal cord into the peripheral nerves. The conus tapers because the grey matter tapers away and the fascicles themselves, having already converged into peripheral nerves, leave no cells to continue the spinal cord. From the conus medullaris to their respective exits, these pre-formed peripheral nerves exist within the **lumbar cistern** (which is just another way of saying the **subarachnoid space** without trabeculae), which is in turn wrapped in dura mater. This **dura-wrapped** construct is known as the **filum terminale**, which terminates at approximately the level of S3.

The **cauda equina** ("horsetail") is so named because of the presence of individual thin peripheral nerves all in one place.

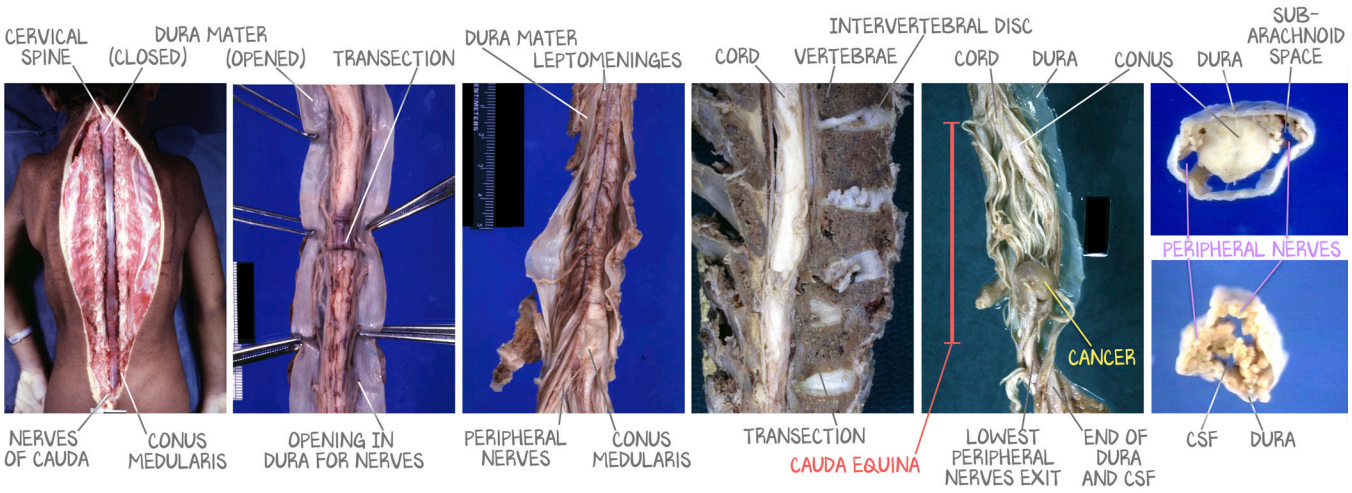

Figure 3.10: Spinal Anatomy and the Cauda Equina
As we move from left to right, different elements of the distal spinal cord are seen. First is a patient who died of a pinealoma. Everything superficial to the dura mater has been removed. The size of the cord is about the same diameter for the entire length, and the dura physically separates the interior of the cord from everything without. The conus medularis and cauda equina are barely visible at the bottom of the dissection. In the second panel, the dura mater has been opened to explore the leptomeninges—the CSF-containing space and blood vessels. Peripheral nerves emerge through the dura mater. The third panel shows the conus medularis and a bundle of peripheral nerves. The fourth panel shows the arrangement of the bones and how little CSF there can be. The fifth panel shows an ependymoma that we don't want you to pay attention to. But this figure demonstrates why these nerves got the name "a horse's tail" (cauda equina). It also demonstrates the filum terminale, the anchoring point for the dura and where the dura mater, leptomeninges, and therefore CSF cease. By the time the nerves reach that point, there is no cord remaining, and the most distal peripheral nerves disappear out the bottom. The two images on the right show the conus medularis running with nerves (top) and what the conus medularis is and will become—tracts of axons (bottom).

Nerve roots continue after the spinal cord ends. Around L2, the spinal cord—the tube surrounded in dura mater—disappears. Each nerve root still exits from between the vertebrae they are named for, and so these are now **peripheral nerves** traveling within the vertebrae to the point of exit. The nerves are still within a space within the vertebral column but have no dura mater to protect them. If there is a **tumor**, **hemorrhage**, or **abscess** growing into the vertebral column, these nerves can be compressed. A herniated disc can compress them as well, but herniations rarely crush all the nerves and usually impinge on the nerve root below it. The risk is increased because there is no spinal cord to resist displacement. However, we want you to think of the aptly-named cauda equina syndrome as an acute condition associated with a medical disease, one that induces a space-occupying lesion to grow and compress the nerves.

The presentation is **saddle anesthesia** (S3–S5), with anesthesia of the genitals, perianal region, and anus. Other sensory deficits can be present, depending on how high the lesion is. Because S3–S5 are at the bottom of the spine, if any of the nerves of the cauda equina are compressed, those lowest will likely be as well. In addition to anesthesia, there may also be **lancinating leg pain**. Treatment is emergent surgical decompression of the nerve(s) causing the symptoms.

What do you think the motor symptoms will be like in cauda equina syndrome?

Because they are peripheral nerves, this will act as a lower motor neuron lesion with hyporeflexia, reduced tone, and possible paralysis.

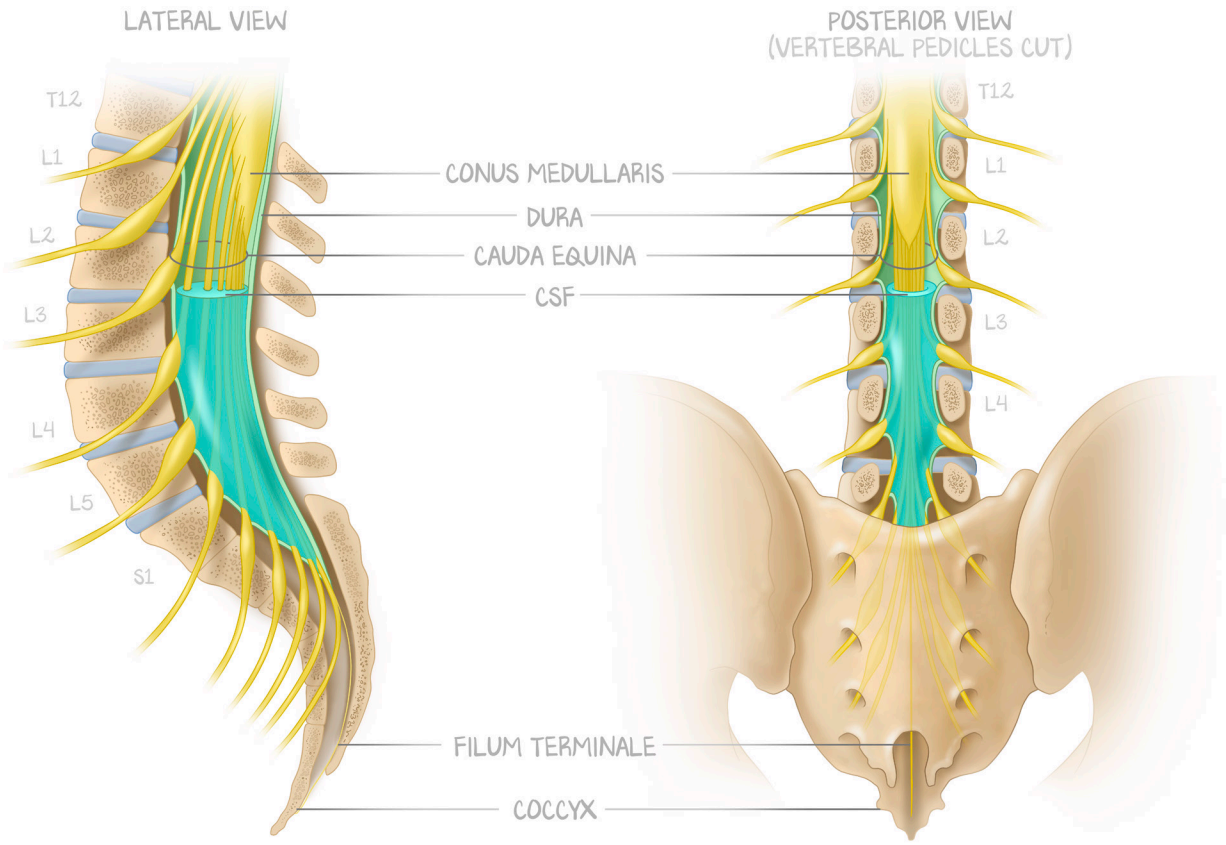

Figure 3.11: Cauda Equina
Illustration of the anatomical position of the cauda equina.

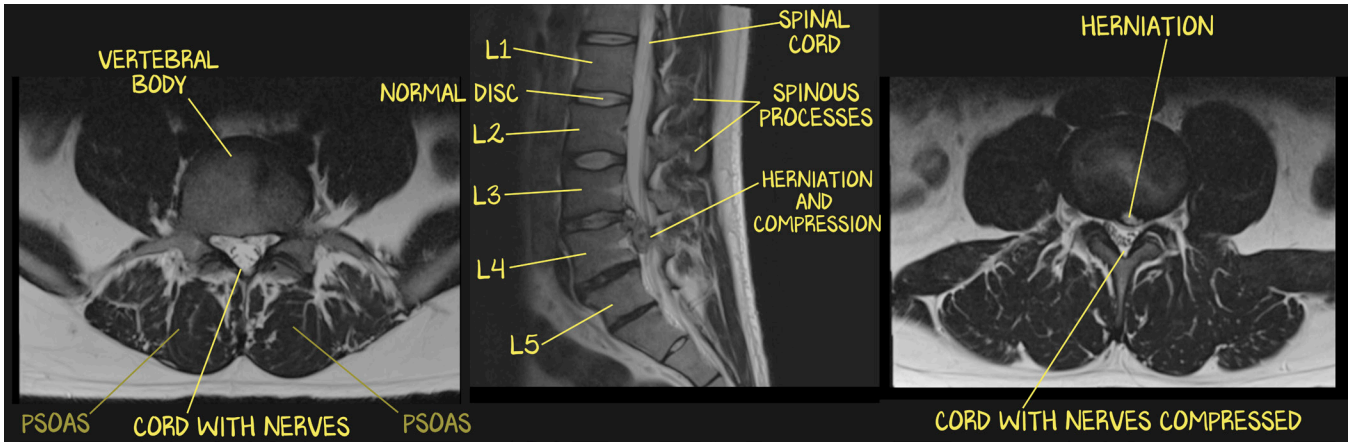

Figure 3.12: Cauda Equina Syndrome
The left panel shows a normal MRI of the spinal cord with white CSF and squiggles of dark, the nerves within the CSF. In the right panel, a herniation of the nucleus pulposus pushes all of the nerves together, and there is hardly any white CSF around the cord. In the center panel, the compression appears to obliterate the lumen of the cord, although the conus medullaris is tapering at L3, just above the compression.

Round 7: Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a **motor-only disease**. It causes the loss of somatic motor neurons. Both upper motor neurons in the frontal cortex and lower motor neurons in the anterior horn are affected, and they are affected haphazardly (asymmetrically, and in the cortex or any vertebral segment). **Autonomic efferent outputs** (the motor outputs of the autonomic nervous system) are **not affected**, thus sparing bowel and bladder function. There is **no sensory impairment**, either. For this lesson, you should already anticipate the symptoms of both upper motor neuron lesions and lower motor neuron lesions in the extremities. But this disease affects all skeletal muscles, including those of the mouth, leading to dysarthria (difficulty speaking) and dysphagia (difficulty swallowing). It is **progressive** and will always claim the patient's life, often as a result of infection. If not, **diaphragmatic paralysis** will lead to respiratory failure. Although there is an association with the gene that codes for copper-zinc superoxide dismutase (SOD1), the pathway appears to be more complicated than just one gene. Mutated *SOD1* results in misfolded proteins and subsequent aggregates. Even in cases where *SOD1* is not mutated, the SOD1 protein aggregates are found. When too many SOD1 aggregates accumulate, the unfolded protein response (another phrase for apoptosis) is initiated. Why the motor neurons are affected the most is unclear. However, much like the Lewy bodies of Parkinson's and frontotemporal dementia, SOD1 aggregates are not specific to the motor neurons, and frontal lobe neurons can be affected as well, leading to cognitive decline and symptoms of frontotemporal lobar degeneration (formerly frontolobar dementia). Few patients live long enough to experience dementia, as the time to death from diagnosis is usually 1–2 years. By the time symptoms appear, all of the motor neurons have likely reached near-toxic levels of SOD1 aggregates, the first to die off merely signaling that the others are close to apoptosis. Thus, novel therapeutics targeting SOD1 clearance are being researched. We'll go into detail on protein aggregate-induced neurodegenerative disorders later in this module.

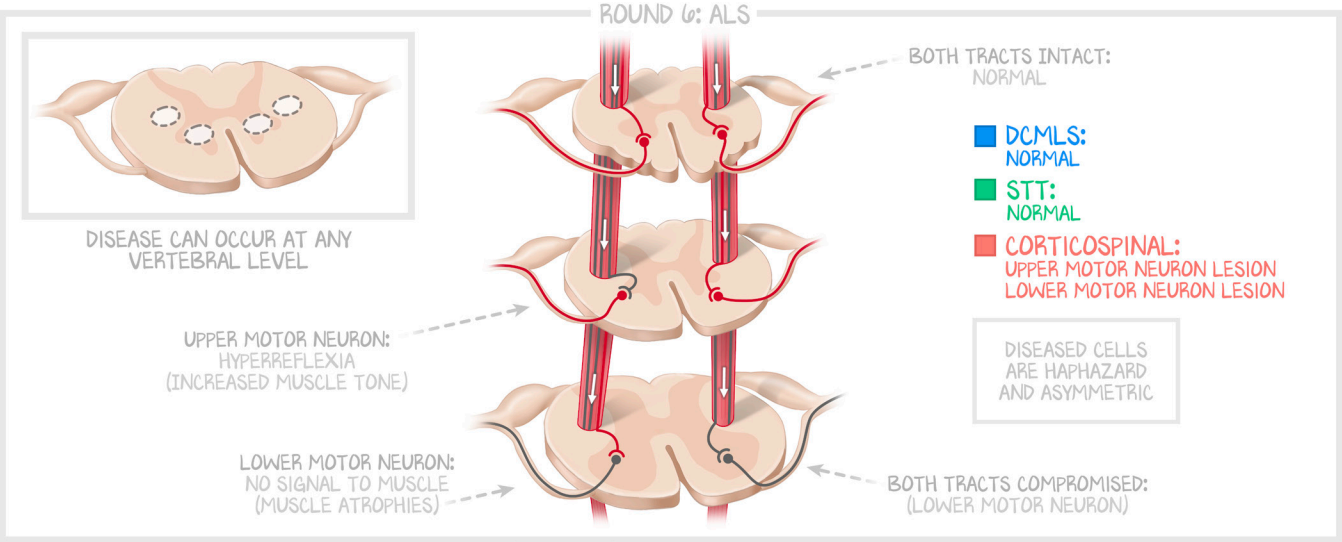

Figure 3.13: Amyotrophic Lateral Sclerosis
Caused by the accumulation of protein aggregates in the cell bodies of neurons, ALS presents with combined upper and lower motor neuron lesion symptoms. Red is intact; grey is lesioned. The tracts are only lesioned because the one neuron and its axon are gone. Thus, you can have many permutations. A red tract on a red nucleus is normal. A red tract on a grey nucleus is a lower motor neuron lesion. A grey tract on a grey nucleus is still a lower motor neuron lesion because the final output is lost. A grey tract on a red nucleus is an upper motor neuron lesion.